Remarks

Reconsideration of this Application is respectfully requested.

Claims 1-9 are pending in the application, with claim 1 being the independent claim.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and further request that they be withdrawn.

The Claimed Invention

The claims are directed to antibodies or fragments thereof against HDGNR10 (CCR5).

Rejections Under 35 U.S.C. § 101

The rejection of claims 1-9 under 35 U.S.C. § 101 was maintained. (Paper No. 20060705, page 2.) Applicants respectfully disagree with the rejection for at least the following reasons.

I. Applicants Asserted A Specific Utility For HDGNR10 In The Disease Rheumatoid Arthritis.

The specification discloses that inhibitors of HDGNR10 (CCR5) may be used to treat rheumatoid arthritis. *See* specification, ¶ [0018], line 7, and ¶ [0094], line 5. Inhibitors of HDGNR10 (CCR5) include antibodies against HDGNR10 (CCR5). *See* specification, ¶ [0088].

Therefore, contrary to the statements on pages 2 and 3 of the final Office Action, Applicants have asserted a specific utility for the claimed invention.

II. The Asserted Utility Is Credible: Post-Filing Date Publications Confirm The Asserted Utility In Rheumatoid Arthritis.

Several post-filing date publications have implicated HDGNR10 (CCR5) in rheumatoid arthritis. *See*, e.g., Gomez-Reino, J.J. et al., *Arthritis Rheum. 42*:989-92 (1999); Mack, M., et al. *Arthritis Rheum. 42*:981-8 (1999); Suzuki, N. et al., *Intl. Immunology 11*:553-559 (1999); and Brühl, H. et al., *J. Immunology 166*:2420-26 (2001) (IDS Documents AR9, AR13, AS19, and AR3, respectively). For example, Suzuki et al. found that T cells expressing CCR5 selectively accumulate in the inflamed joints of patients with rheumatoid arthritis.

Moreover, just as the specification states, e.g., at page 5, the authors of these publications indicate that a protein of the invention would be a good target for treating rheumatoid arthritis. See, e.g., Gomez-Reino et al., p. 991 ("*blocking of CCR5 with specific monoclonal antibodies* and synthetic peptides, or by other means, could potentially be a promising *therapeutic approach*." (emphasis added)). The information in Brühl et al., Gomez-Reino et al., Mack et al. and Suzuki et al., confirms the credibility of using HDGNR10 (CCR5) antibodies to treat rheumatoid arthritis. Thus, these publications by others confirm the asserted utility of HDGNR10 (CCR5).[1]

[1] Moreover, the publications by Brühl et al., Gomez-Reino et al., Mack et al. and Suzuki et al. support the credibility of the asserted inflammation-related utilities for HDGNR10 (CCR5). *See* specification, *e.g.*, ¶ [0018], line 5.

III. Knowledge Of HDGNR10 Chemokine Ligands Is Not Necessary To Identify HDGNR10 Molecules That Are Useful In Rheumatoid Arthritis

The Examiner cited Chuntharapai, *Methods Enzymol. 288*:15-27 (1997), for the proposition "that the production of therapeutic (blocking) antibodies to chemokine receptors *required* knowledge of the identity of at least one agonist thereto." (Paper 20060705, p.4 (emphasis added).) Applicants respectfully disagree.

Nowhere does Chuntharapai (1997) state that the identity of a chemokine receptor agonist is *required* to identify therapeutic or blocking antibodies. Even assuming, arguendo, that Chuntharapai (1997) did make such a statement, alternative methods were also available in June 1995, the priority date of the subject application, that did not require knowledge of a receptor agonist.

For example, one could identify antagonistic anti-HDGNR10 antibodies that are useful to treat rheumatoid arthritis in an experimental model for the disease.[2] Several models for rheumatoid arthritis existed in June 1995. *See*, e.g., Houri, et al. *Curr. Opinion Rheumatology 7*:210-205 (May 1995) (review of recent advances in rheumatoid arthritis research using non-spontaneous animal models); O'Sullivan et al., in *Mechanisms and models in rheumatoid arthritis*, 1st Ed., Henderson et al., eds., Academic Press Inc, San Diego, CA (1995), pp. 471-491 (review of spontaneous animal models of arthritis); Rubin et al., *Lab. Invest. 57*:524-534 (1987) (collagen-induced arthritis in the rhesus monkey as a model for rheumatoid arthritis); 'T Hart et al., *Clin. Exp. Immunol. 83*:375-78 (1991) (rhesus monkey model).[3] Thus, to verify the

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[2] Additional alternative methods may have existed for identifying antagonistic antibodies.

[3] Copies of these documents, as well as the newly cited documents in the remainder of the Reply, were provided with the Information Disclosure Statement (IDS)

therapeutic usefulness of anti-HDGNR10 antibodies, the artisan could have used one or more of these experimental models.

In addition, prior to testing in the animal model, experiments could be carried out to improve the probability that antibodies selected for testing would in fact be useful for treating rheumatoid arthritis. For example, since a correlation exists between antibody binding affinity and blocking activity (see, e.g., Chuntharapai, *J. Immunology 152*:1783-89 (1994), abstract and paragraph spanning pages 1788 and 1789), one could select antibodies that have high binding affinity (and no cross-reactivity) to increase the likelihood that the antibodies being tested in an animal model will turn out to be therapeutic.

Significantly, it would *not* have been necessary to know the identity of a HDGNR10 agonist to identify, using an experimental model, those antibodies that are useful for rheumatoid arthritis.

IV. The Law Requires Only A Single Utility

The Examiner further alleges that the asserted use of agonists of HDGNR10 (CCR5) for treating T cell-mediated autoimmune diseases (see paragraph [0016] of the instant specification) is not credible and is in conflict with the asserted utility for treating rheumatoid arthritis, and concludes that the invention is therefore not supported by a credible utility. (Paper 20060705, pp.5-6.) Applicants respectfully disagree. As outlined below (see Section V), one of skill in the art would recognize and find credible

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filed August 9, 2006 in parent Appl. No. 10/127,764, and these documents are also listed on the IDS filed herewith.

situations in which an HDGNR10 agonist could be useful in treating a T cell-mediated autoimmune disease.

Applicants first wish to point out that they "need only make ***one*** credible assertion of specific utility for the claimed invention to satisfy 35 U.S.C. § 101 and 35 U.S.C. § 112; ***additional statements of utility, even if not 'credible,' do not render the claimed invention lacking in utility***." MPEP 2107.02 (I) at 2100-37 (emphasis added); *see also In re Gottlieb*, 140 USPQ 665, 668 (CCPA 1964) ("Having found that the antibiotic is useful for *some* purpose, it becomes unnecessary to decide whether it is in fact useful for the other purposes 'indicated' in the specification as possibly useful.").. In fact, the Federal Circuit has stated that:

> To meet the utility requirement, the Supreme Court has held that a new product or process must be shown to be "operable" - that is, it must be "capable of being used to effect the object proposed." Our cases have not, however, interpreted this language . . . to mean that a patented device must accomplish ***all*** objectives stated in the specification. On the contrary, "[w]hen a properly claimed invention meets at least one stated objective, utility under § 101 is clearly shown."

Carl Zeiss Stiftung v. Renishaw PLC, 20 USPQ2d 1094, 1100 (Fed. Cir. 1991) (citations omitted) (quoting *Raytheon Co. v. Roper Corp.*, 220 USPQ 592, 598 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 835 (1984)); *see* also, MPEP § 2107.02 (IV) at 2100-41 ("Where the asserted specific and substantial utility is not credible, a *prima facie* showing of ***no*** specific and substantial credible utility must establish that it is more likely than not that a person skilled in the art would not consider credible ***any*** specific and substantial utility asserted by the applicant." (emphasis added)).

The use of antagonists of HDGNR10 (CCR5) to treat inflammatory conditions, including rheumatoid arthritis, was credible as of the priority date based on knowledge in the art. *See* specification, ¶ [0018] (disclosing use of HDGNR10 antagonists to treat chronic and acute inflammation and rheumatoid arthritis). It was known in the art that at least some chemokines are involved in inflammatory conditions and/or the trafficking of lymphocyte subsets that were known or were believed to be key players in inflammatory diseases. *See, e.g.*, Schall, T.J., *Cytokine 3*:165-183 (1991), pp. 175, col. 2 to p 176, col. 1, and p. 178, col. 2 to p. 179, col. 2 (IDS Document AT18); and specification, ¶ [0009]. In addition, it was believed that rheumatoid arthritis, one of the specific conditions listed in the specification, is partially the result of an inflammatory reaction, and that chemokine expression is associated with rheumatoid processes. *See, e.g.*, Schall et al. Moreover, it was known that antibodies against chemokine receptors could be used to inhibit the receptors. *See, e.g.*, Murphy, *Annu. Rev. Immunol. 12*:593-633 (1994) (IDS Document AT14).

Given the knowledge in the art as of the priority date, and Applicants' disclosure that HDGNR10 is a chemokine receptor, it would have been *reasonable* to conclude that antibodies against HDGNR10 (CCR5) would be useful for diagnosing or inhibiting rheumatoid arthritis or another inflammatory condition.

In addition, the use of HDGNR10 (CCR5) antagonists to treat rheumatoid arthritis has been confirmed by post-filing date publications. (*See* Section II, supra; and Reply dated April 25, 2006, at pages 5-7, incorporated herein by reference.) Therefore, Applicants have complied with the requirements of 35 U.S.C. § 101 by specifically asserting that use, e.g., in paragraph [0018] of the specification.

Moreover, Applicants point out that the claims are not directed to an agonist of HDGNR10, nor are they directed to a method of using an HDGNR10 agonist. Therefore, the credibility, or alleged lack thereof, of using agonists to treat T cell-mediated autoimmune diseases is *irrelevant* to the pending claims as long as another specific and credible utility is disclosed or well-established. *See* MPEP § 2107.02 (I) at 2100-37 to 2100-38 ("Office personnel should also be especially careful not to read into a claim unclaimed results, limitations, or embodiments of an invention. Doing so can inappropriately change the relationship of an asserted utility to the claimed invention and raise issues ***not relevant*** to examination of that claim." (citations omitted) (emphasis added)). As discussed above (see Sections I-II), at least one disclosed utility is specific and credible, and this utility was subsequently confirmed by post-filing date publications.

V. HDGNR10 Agonists May Be Useful To Treat T Cell-mediated Autoimmune Disease.

The Examiner stated that post-filing date art has shown that agonists of HDGNR10 (CCR5) cannot be used to treat T cell-mediated autoimmune diseases. (Paper 20060705, pp. 5-6.)

Although the veracity of the Examiner's assertion is irrelevant since Applicants "need only make ***one*** credible assertion of specific utility for the claimed invention to satisfy 35 U.S.C. § 101 and 35 U.S.C. § 112," and "***additional statements of utility, even if not 'credible,' do not render the claimed invention lacking in utility,***" in order to be

fully responsive, Applicants respectfully point out that there are situations in which HDGNR10 agonists may be useful for treating a T cell-mediated autoimmune disease.[4]

First, HDGNR10 (CCR5) agonists and antagonists may be useful to treat a T cell-mediated autoimmune disease at different stages of the disease process. This appears to be true for IL-12 in an animal model for polyarthritis (Joosten et al., *J. Immunology 159*:4094-4102 (1997)) and for IL-10 in an animal model for systemic lupus erythematosus (Yin et al., *J. Immunology 169*:2148-55 (2002)). As described below, in both diseases, *removing* the relevant cytokine ameliorates signs and/or symptoms during one stage of disease, while *providing* the relevant cytokine ameliorates signs and/or symptoms during another stage of the disease. Like IL-10 and IL-12, agonists of HDGNR10 (CCR5) are cytokines (the name chemokine stands for "chemotactic cytokine," see, e.g., Luster, *New Eng. J. Med. 338*:436-45 (1998)), and moreover, they are intimately involved with immune regulation. Therefore, it is credible, based on the data discussed below, that an agonist of HDGNR10 (CCR5) could ameliorate symptoms at some stage of a T cell-mediated autoimmune disease.

Joosten and colleagues studied the role of IL-12 in collagen-induced arthritis. Joosten et al., *J. Immunology 159*:4094-4102 (1997). Collagen-induced arthritis (CIA) in mice and rats is an accepted model for polyarthritis, and it shares histopathological features with human rheumatoid arthritis (RA). *Id.* at p. 4094, col. 2. Joosten et al. found that IL-12 treatment exacerbates early CIA, whereas IL-12 suppresses disease in established CIA. *Id.*, e.g., abstract. The corollary was also found: anti-IL-12 antibodies

[4] Applicants have described three situations; however, additional situations may exist in which an HDGNR10 (CCR5) agonist would be useful for treating a T cell-mediated autoimmune disease.

administered early in CIA lowered the incidence and severity of disease, while treatment with antibodies during established CIA exacerbated disease. *Id.*

Similar data exists for IL-10. Particular mouse strains develop a spontaneous form of lupus that serves as a model for the human autoimmune disease systemic lupus erythematosus (SLE). Yin et al., *J. Immunology 169*:2148-55 (2002); Ishida et al., *J. Exp. Med. 179*:305-10 (1994). Previous studies in a mouse model and in SLE patients had shown that anti-IL-10 antibody improved biological markers of disease. Llorente et al., *Arthritis Rheum. 43*:1790-1800 (2000); Ishida et al., *J. Exp. Med. 179*:305-10 (1994). However, in a later study, Yin and colleagues found that IL-10 double negative mice had much more severe disease and higher mortality than littermates with one or two intact IL-10 genes. Yin et al., e.g., abstract. In addition, they found that administration of recombinant IL-10 to IL-10 intact mice reduced the level of pathogenic anti-dsDNA antibody early in disease. *Id.*, p. 2154, col. 1. Yin et al. concluded that IL-10 has dual effects at different stages of disease: a suppressive effect on lupus at an early disease stage, and a pathogenic effect at later disease stages. *Id.,* e.g., p.2154, col. 2 to p. 2155, col. 1.

Thus, both IL-12 and IL-10 can be either therapeutic or pathogenic in a single T cell-mediated autoimmune disease depending on the stage at which they are administered. Furthermore, one of skill in the art would find it credible that HDGNR10 (CCR5) agonists can be either therapeutic or pathogenic in T-cell mediated autoimmune disease.

Second, scientists have proposed using HDGNR10 (CCR5) agonists to induce tolerance to self antigens to prevent or treat a T cell-mediated autoimmune disease.

DePaolo et al., *J. Immunology 173*:314-20 (2004). Self antigens administered orally have been used to induce tolerance in several experimental models of autoimmune disease. Reviewed in: Weiner, H.L., *Immunol. Today* 18:335-43 (1997). One of these models is experimental autoimmune encephalomyelitis (EAE), which is a model for the T cell-mediated autoimmune disease multiple sclerosis (MS). DePaolo et al., p. 314, col. 1. Using CCR5 double knock-out mice, DePaolo et al. showed that CCR5 is required to induce oral tolerance. *Id.*, e.g., p. 318, col. 2. In addition, they showed that two CCR5 agonists (CCL4/MIP-1β and CCL5/RANTES) are up-regulated during the induction of oral tolerance. *Id.*, p. 319. The authors conclude by saying "the use of a CCR5 agonist in conjunction with high dose oral [antigen] might be able to tip the GALT cytokine balance during ongoing autoimmune disease toward anti-inflammatory and result in a diminution of autoreactivity." *Id.*, p. 320. col. 1.

Third, HDGNR10 (CCR5) agonists could be used to shift a pathogenic Th2-type autoimmune response to a nonpathogenic Th1-type response in certain T cell-mediated autoimmune diseases. Singh et al., *Immunologic Res.* 20:147-61 (1999), p. 154, col. 2. ("It is important to note that in experimental animal models, a number of diseases can be prevented by switching the immune response from . . . Th2 to Th1-type.") Th2-type diseases in which HDGNR10 (CCR5) agonists may be useful include systemic sclerosis (scleroderma) and drug-induced autoimmune disease. Szeto et al., *Immunology 100*:217-24 (2000), paragraph spanning pp. 217 and 218; Wu et al., *Curr. Pharmaceut. Design 10*:899-913 (2004), at p. 900, col. 1. and p. 907, col. 1. A switch from a Th2- to a Th1-type response has been implicated as the cause for attenuation of drug-induced

autoimmune disease during spontaneous remission and during levamisole treatment. Wu et al., p. 900, col. 1; Szeto et al., e.g., abstract.

In order for HDGNR10 (CCR5) agonists to be useful in Th2-type diseases, they must induce Th1 differentiation. Evidence that CCR5 agonists induce Th1 differentiation comes from several studies. Luther et al. summarized some of this evidence in a 2001 review article on chemokines. Luther et al., *Nature Immunol. 2*:101-107 (2001), p. 104, 1st col. Luther et al. conclude that more work is needed, but "[i]t seems likely that, when high amounts of CCL3, CCL4, or CCL5 are present at the site of T cell activation, a cell-mediated Th1-type response will be favored." *Id.*, col. 2.[5] Due to the regulatory balance between Th1- and Th2-type responses, driving the response towards a Th1-type response causes suppression of a Th2-type response. *See*, e.g., Wu, at page 899, col. 2. Therefore, it would be credible that HDGNR10 (CCR5) agonists could be used to attenuate or improve disease symptoms in Th2-type autoimmune diseases such as systemic sclerosis (scleroderma) and drug-induced autoimmune disease by driving the response towards a Th1-type.

The data discussed above shows that one of skill in the art would find credible the assertion that HDGNR10 agonists could be used to treat T cell-mediated autoimmune disease. However, Applicants maintain that the credibility, or alleged lack thereof, of this utility is irrelevant to the claimed invention because another specific, disclosed utility is credible and has been confirmed. (*See* Sections I and II, supra).

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[5] CCL3/MIP-1α, CCL4/MIP-1β, and CCL5/RANTES are all HDGNR10 (CCR5) ligands.

VI. Summary

As discussed above, the specification specifically discloses that HDGNR10 antagonists are useful to treat rheumatoid arthritis. Moreover, pre- and post-filing date publications support the credibility of this utility. In view of the claimed invention, and the fact that at least one utility exists for the invention as claimed, Applicants have satisfied the requirement under 35 U.S.C. § 101.

Even assuming, arguendo, that the Examiner has established a prima facie showing that the claimed invention lacks any utility, Applicants respectfully submit that they have rebutted the Examiner's showing by proffering sufficient evidence to lead one skilled in the art to conclude that HDGNR10 has a specific, credible utility.

In view of the facts set out above, Applicants submit that a skilled artisan would not reasonably doubt that the claimed polypeptides can be useful in rheumatoid arthritis. As such, Applicants assert that the presently claimed invention possesses a credible utility that constitutes a patentable utility under 35 U.S.C. § 101. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §101 be reconsidered and withdrawn.

Rejections Under 35 U.S.C. § 112 – Enablement

Claims 1-9 were rejected under 35 U.S.C. § 112, as the specification allegedly fails to teach how to use the invention, for the reasons given above in connection with the utility rejection.

For the reasons discussed above in reply to the utility rejection, Applicants assert that the claimed invention is supported by a specific and credible utility. Therefore,

since the claimed invention complies with the utility requirement of 35 U.S.C. § 101, the rejection under 35 U.S.C. § 112, first paragraph, based on the alleged lack of utility of the claimed invention, should be withdrawn.

Additionally, claim 8 was rejected under 35 U.S.C. § 112, as the specification allegedly fails to teach how to identify the claimed antagonistic antibody. (Paper 20060705, pp. 6-7.) The Examiner cited Chuntharapai, *Methods Enzymol. 288*:15-27 (1997) as evidence that not all antibodies that bind an extracellular domain of a chemokine receptor are antagonistic, and stated that it is not clear how an antagonistic antibody can be identified without being able to measure the agonistic activity of the receptor. (Paper 20060705, p. 7.) Applicants respectfully disagree.

As stated above in response to the utility rejection (see section III, *supra*), at least one alternative means existed for identifying antagonistic antibodies that did not require knowledge of the receptor agonist. As discussed above, one could choose high affinity anti-HDGNR10 (CCR5) antibodies and test these in an animal model for rheumatoid arthritis to choose antagonistic antibodies that are therapeutically useful.

Significantly, it would *not* have been necessary to know the identity of a HDGNR10 agonist to identify, using an experimental model, those antibodies that are antagonistic and therefore useful for inhibiting, e.g., rheumatoid arthritis. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claim 8 under 35 U.S.C. § 112.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and further request that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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